REMARKS

AMENDMENTS TO THE SPECIFICATION

The Title of the specification was amended to delete "and SPLICE VARIANT THEREOF" at the end of the Title, and to append "SPLICE VARIANT" after "GLYCINE RECEPTOR ALPHA SUBUNIT" and "sv" after "HGRA4". These amendments were made solely to make the Title consonant with the claimed invention. Support for these amendments may be found in the paragraph beginning on line 24 on page 39, original Claim 1, and pending Claims 20-40. No new matter has been added.

STATUS OF THE CLAIMS:

Claims 20 and 37 were amended.

Claims 20 to 40 are pending.

Claim 20(e) was amended to append the ", wherein said encoded polypeptide has glycine receptor activity" limitation. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim. Support for this amendment may be found on pages 39 and 40 of Applicants application, and throughout the specification as originally filed. Applicants reserve the right to prosecute Claims 20(e) as originally presented in related applications. Applicants right to equivalents of Claim 20 is reserved. No new matter has been added.

Claim 20(f) was amended to delete the "(antisense)" term, in addition to correct the incorrect spelling of the "complimentary" term to its correct spelling of "complementary". Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim. Applicants reserve the right to prosecute Claims 20(f) as originally presented in related applications. Applicants right to equivalents of Claim 20 is reserved. No new matter has been added.

Claim 20(f) was further amended to delete the "or fragment thereof" limitation. Claim 20(f) was further amended to append the "or" term in between "(d)" and "(e)" in order to take into account the deletion of the "or fragment thereof" limitation. Applicants assert that these amendments were not made to overcome any issues related to the patentability of this claim. Applicants reserve the right to prosecute Claims 20(f) as originally presented in related applications. Applicants right to equivalents of Claim 20 is reserved. No new matter has been added.

Claim 37 was amended to append the CLUSTALW parameters after the "CLUSTALW global sequence alignment" phrase. Support for this amendment may be found on page 68 of the specification, and throughout the application as originally filed. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim. Applicants reserve the right to prosecute Claims 37 as originally presented in related applications. Applicants right to equivalents of Claim 37 is reserved. No new matter has been added.

Claim 37 was further amended to append the "wherein said polynucleotide further encodes a polypeptide having glycine receptor activity". Support for this amendment may be found on pages 39 and 40 of Applicants application, and throughout the specification as originally filed. Applicants assert that this amendment was not made to overcome any issues related to the patentability of this

claim. Applicants reserve the right to prosecute Claim 37 as originally presented in related applications. Applicants right to equivalents of Claim 37 is reserved. No new matter has been added.

I. Miscellaneous

a. Public Access to ATCC Deposit No. PTA-2966

Applicants representative hereby gives the following assurance by signature below:

Bristol-Myers Squibb Company, an assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209. This deposit comprises the cDNA sequence encoding the HGRA4sv polypeptide of the present invention. The deposit for HGRA4sv was made on January 24, 2001, and given ATCC Accession Number PTA-2966. In accordance with MPEP 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Number PTA-2966 will be irrevocably removed upon the grant of a patent based on the captioned application, except as permitted under 37 C.F.R. § 1.808(b).

A copy of the ATCC Deposit receipt for Accession Number PTA-2966 is enclosed herewith.

b. Relevance of References Submitted

The Examiner states that the relevance of references AS, AT, AA, and AB submitted on Applicants PTO-1449 cannot be assessed "as the references are amino acid or nucleotide sequences, and no indication of relevance or alignment to the disclosed sequences has been provided". Applicants assert that each of these references, with the exception of reference AB, are present in the Genbank ENTREZ database and their relevance to the claimed invention would have been readily apparent in the Examiners BLAST search. However, in an effort to assist the Examiner's examination, Applicants enclose herewith the alignments of each of the referenced sequences to the HGRA4sv nucleotide (SEQ ID NO:3) or amino acid sequence (SEQ ID NO:4) as applicable. An alignment of the HGRA4sv polypeptide sequence with reference AS is provided in Exhibit A; an alignment of the HGRA4sv polypeptide sequence with reference AT is provided in Exhibit B; and an alignment of the HGRA4sv polypeptide sequence with reference AA is provided in Exhibit C.

Applicants reference AB is the sequence of an Incyte Pharmaceuticals, Inc. clone that was used to identify the HGRA4sv sequence of the present invention, clone ID No. G1934909 (see Example 3). The sequence of clone ID No. G1934909 was made available to Applicants on account of Applicants being a registered Subscriber to the LifeSeq database provided by Incyte

Pharmaceuticals, Inc., and was not publicly available prior to Applicants filing date. Nonetheless, Applicants have included an alignment of the HGRA4sv polynucleotide sequence with reference AB (see Exhibit D) for the Examiner's consideration.

c. Common Ownership

The Examiner reminds Applicants of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the "applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a)."

Applicants representative points out to the Examiner that all of the pending claims were commonly owned by Bristol-Myers Squibb Company and that 35 U.S.C. 103(c) and 35 U.S.C. 102(f) or (g) do not apply under 35 U.S.C. 103(a). In confirmation of the latter, Applicants specifically bring to the attention of the Examiner that each of the inventors have assigned their right and title to Bristol-Myers Squibb Company. See Assignments recorded May 9, 2002, on reel 012890, frame 0940, in reference to the instant specification.

II. Rejections under 35 U.S.C. § 101

a. The Examiner has rejected 20 to 40 under 35 U.S.C. § 101, for failure to demonstrate a credible, substantial, specific, or a well-established utility. More particularly, the Examiner alleges that "The asserted utilities are not considered to be substantial because the specification fails to disclose any particular function, or biological significance *directly* associated with the instant HGRA4, nor any particular gene mutation, or any disease or condition associated with the HGRA4".

Applicants disagree. In response to the Examiners allegation that the instant disclosure does provide sufficient objective evidence of any activity for the encoded protein, Applicants wish to point out to the Examiner that the patent laws do not require that a specification actually demonstrate use of a claimed invention. Rather, it is established law that a disclosure is enabling so long as it contains information which would lead one of ordinary skill in the art to *reasonably believe* the claimed invention has utility. *In re Barr*, 170 U.S.P.Q. 330 (C.C.P.A. 1971). In the absence of evidence or apparent reason why the claimed polynucleotides do not possess the disclosed utility, the allegation of utility in the specification *must* be accepted as correct. *Ex parte Krenzer*, 199 U.S.P.Q. 227 (Pat. Off. Bd. App. 1978). Applicants assert that one skilled in the art would reasonably believe

that HGRA4sv is a novel splice variant of a new member of the human glycine receptor family of proteins based upon the evidence provided in the instant specification and would have the utilities asserted by Applicants specification.

Specifically, Applicants specification teaches that the HGRA4sv polypeptide is a splice variant of the human ortholog of the mouse glycine receptor 4 protein (GRA4; Genbank Accession No. gi|817957; SEQ ID NO:12; see the paragraph beginning on page 39, line 24 of applicants specification) which functions in "modulating inhibitory neurotransmission which is essential for voluntary motor control, flex responses and sensory signal processing" (see paragraph beginning on page 43, line 18). More particularly, Applicants specification teaches that HGRA4sv is associated with "neural disorders", "a disorder affecting the peripheral nervous system", "a degenerative neural disorder", "a neural disorder related to chronic peripheral neuropathies", "modulating neurite outgrowth, [om]modulating the acrosome reaction, and preventing, ameliorating, and treating hyperplexia, spastic paraparesis, and memory deficit in inhibitory learning avoidance" (see pages 7 and 8). Applicants specification also teaches that HGRA4sv is useful for eliciting any of the following effects "...(1) increased survival time of neurons in culture; (2) increased sprouting of neurons in culture or in vivo; (3) increased production of a neuron-associated molecule in culture or in vivo, e.g., choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction in vivo." (see paragraph beginning on page 183, line 22).

Applicants point out to the Examiner that each of these asserted utilities are credible, substantial, and specific to the HGRA4sv protein of the present invention.

Applicants believe the asserted utilities for HGRA4sv are credible based upon the totality of the evidence presented in Applications specification. Specifically, Applicants specification teaches that HGRA4sv shares 76.8% identity and 82.2% similarity with the human glycine receptor alpha-1 subunit protein; 84.4% identity and 78.7% similarity with the human glycine receptor alpha 3 subunit protein; 80.6% identity and 86.5% similarity with the human glycine receptor alpha-2 subunit protein; and 97% identity and 96% similarity with the mouse glycine receptor subunit alpha 4 protein (see paragraph beginning on page 38, line 26). Applicants assert that one skilled in the art would appreciate that such high identity alone is sufficient evidence to demonstrate that HGRA4sv is a novel glycine receptor. Applicants point out to the Examiner the teachings of Matzenbach et al (J. Biol. Chem., 269(4):2607-2612 (1994); submitted with Applicants September 16th, 2002 IDS form PTO-1449). Matzenbach et al discloses the percent identity between various mouse and human glycine receptors to each of the known glycine receptor homologs and their corresponding orthologs.

It is noted that the percent identity shared between the various glycine receptors is all within a range of 80% identity and above (see page 2610 in particular). Applicants point out to the Examiner that the percent identity shared between the HGRA4sv protein of the instant specification to the known glycine receptor homologs is within this range. Importantly, the newly identified mouse glycine receptor 4 protein discussed in the Matzenbach et al paper was described as being a member of the glycine receptor family based primarily upon its high percent identity to the other glycine receptors (see Discussion). In consideration of the >80% identity between HGRA4sv with the human glycine receptors 2 and 3, combined with the 97% identity to the mouse glycine receptor 4, Applicants assert that one skilled in the art would credibly believe that the HGRA4sv protein is a glycine receptor and represents the human ortholog of the mouse glycine receptor 4 protein.

Additional supporting evidence that HGRA4sv is a human glycine receptor is provided in Applicants specification. Specifically, Applicants specification provides detailed teachings indicating both the presence and location of domains that are characteristic of glycine receptor family members, such as the presence of the "ligand binding sites located at about amino acid 208 to about amino acid 209, and from about amino acid 259 to about amino acid 263 of SEQ ID NO:4" (see Figure 2A-B legend on page 10); the presence of "three transmembrane domains (TM1 to TM3) located from about amino acid 269 to about amino acid 295 (TM1), from about amino acid 302 to about amino acid 319 (TM2), and/or from about 334 to about amino acid 357 (TM3) of SEQ ID NO:4" (see Figure 2A-B legend on page 10); the presence of "conserved cysteine residues located at amino acid 172, 186, 247, and 258 of SEQ ID NO:4" (see Figure 2A-B legend on page 10); and the presence of the "neurotransmitter gated ion channel domain from about amino acid 44 to about amino acid 355 of SEQ ID NO:4" (see paragraph beginning on page 53, line 11). The presence of these domains represents further confirmation that one skilled in the art would credibly believe that HGRA4sv is a human glycine receptor based upon the teachings of Applicants specification as originally filed, particularly in conjunction with the striking identity between HGRA4sv with glycine receptors known in the art.

Applicants also point out that even the Examiner acknowledges the credibility of Applicants assertions that HGRA4sv is a human glycine receptor based upon the Examiners statement that "...it is likely that the HGRA4 is a glycine receptor alpha subunit" (see page 4 of the Office Action).

Applicants credible identification of HGRA4sv as being a human glycine receptor is significant considering known glycine receptors have been positively associated with various diseases and disorders and thus would meet the credible, substantial, and specific utility or well-

established utility requirement. Specifically, Applicants specification teaches that "Mutations in the glycine receptor alpha 1 gene have been shown [to] cause hereditary hyperkplexia and spastic paraparesis (Elmslie et al., 1996; Shiang et al., 1993)" (see page 2 of specification; see also Elmslie et al, J. Med, Genet. *33*, 435-436 (1996); Shiang et al, Nature Genet. *5*, 351-357 (1993); submitted concurrently herewith). Moreover, Applicants specification also teaches that glycine receptors play major roles in nervous system biology by pointing out that "Studies on antagonists and partial agonists of the glycine receptor have suggested that the glycine receptor has a role in memory deficits in inhibitory avoidance learning (Viu et al., 2000). Other studies have shown that glycine receptors can modulate neurite outgrowth in developing mouse neurons (Tapia et al., 2000)." (see page 2 of specification; see also Viu et al, Neurobiol. Learn Mem. *74*, 146-160 (2000); and Tapia et al, Neuroreport *11*, 3007-3010 (2000); submitted concurrently herewith). Applicants assert that one skilled in the art would credibly believe that HGRA4sv would have the utilities asserted in Applicants specification based upon the well-known associations of human glycine receptors to disorders consonant with the neurological disorders ascribed to HGRA4sv by Applicants specification.

Applicants also believe that the asserted HGRA4sv utilites are well-established based upon the teachings of Rappold-Hoerbrand (International Publication No. WO 00/58461; submitted with Applicants September 16th, 2002 IDS form PTO-1449). Rappold-Hoerbrand discloses a molecule, referred to as an ataxia associated protein (SEQ ID NO:2), that is 100% identical to Applicants HGRA4 polypeptide (SEQ ID NO:2; encoded by the polynucleotide provided as SEQ ID NO:1) which represents a splice variant of Applicants claimed HGRA4sv (SEQ ID NO:4; encoded by the polynucleotide provided as SEQ ID NO:3). Rappold-Hoerbrand teaches that the disclosed gene is positively associated with ataxia based upon the confirmation that the genomic region for the HGRA4 gene, referred to as PAC clone 1055C14 by Rappold-Hoerbrand, covers a breakpoint between Xp22 and Xq22 from a ten year old boy suffering from slight mental retardation and severe cerebellar ataxia (see Example 1 and page 4 of Rappold-Hoerbrand). The latter determination was confirmed by FISH-analysis.

In addition, Rappold-Hoerbrand also demonstrated that the HGRA4 gene was directly affected by the Xp22 and Xq22 chromosome breakpoint by isolating the exons encoding the HGRA4 gene and using FISH analysis on metaphase spreads of the patients mother (presenting with a normal phenotype) compared to that of the boy's rearranged chromosome. The results showed a FISH signal in Xq22 as well as a cross-hybridization to Xq28 on the mother's metaphase spreads, while a strong

signal was observed on Xp22 and the cross-hybridization signal, but with a weak signal in Xq22 on the boy's metaphase spreads. Rappold-Hoerbrand states that "[T]his shows clearly that the breakpoint of the patient resides within the genomic locus of the ataxia gene".

Gene mapping of disease loci and chromosomal aberrations has become a highly effective means of identifying genes associated with disorders in the art. Applicants point out that one skilled in the art would clearly appreciate that HGRA4 has a credible, substantial, and specific utility or a well-established utility based upon the teachings of Rappold-Hoerbrand. Since the HGRA4sv composition of the present invention represents a splice variant of HGRA4, Applicants assert that it also has a credible, substantial, and specific utility or well-established utility.

Applicants point out to the Examiner that the asserted utilities of HGRA4sv, discussed *supra,* are directly analogous to the ataxia utility ascribed to HGRA4 by Rappold-Hoerbrand. Specifically, Rappold-Hoerbrand teaches that "Ataxia in general describes the inability of a patient to properly corrdinate his or her movements and is caused by neuronal defects. The autosomal dominant forms mostly represent neurodegenerative disorders and are characterized by the selective loss of neurons..." (see page 1 of Rappold-Hoerbrand). Moreover, Rappold-Hoerbrand also teaches that among the known ataxias, "Clinical manifestations vary considerably within each genetically defined type..." (see page 2 of Rappold-Hoerbrand). The latter is important as it suggests that there is not a single, well-defined phenotype for ataxias recognized in the art, but rather the ataxias manifest in a variety of closely related phenotypes with neurodegeneration and movement aberrations representing a common underlying theme. Applicants specification teaches that the HGRA4sv polypeptide functions in "modulating inhibitory neurotransmission which is essential for voluntary motor control, flex responses and sensory signal processing" (see paragraph beginning on page 43, line 18 of Applicants specification). More particularly, Applicants specification teaches that HGRA4sv is associated with "neural disorders", "a disorder affecting the peripheral nervous system", "a degenerative neural disorder", "a neural disorder related to chronic peripheral neuropathies", "modulating neurite outgrowth, [om]modulating the acrosome reaction, and preventing, ameliorating, and treating hyperplexia, spastic paraparesis, and memory deficit in inhibitory learning avoidance" (see pages 7 and 8). Applicants specification also teaches that HGRA4sv is useful for eliciting any of the following effects "...(1) increased survival time of neurons in culture; (2) increased sprouting of neurons in culture or in vivo; (3) increased production of a neuron-associated molecule in culture or in vivo, e.g., choline acetyltransferase or

acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction in vivo." (see paragraph beginning on page 183, line 22).

Applicants assert that these utilities are "specific" since they are specific to neurodegenerative disorders, and not just any disorder. Applicants also assert that these utilities are "substantial" since neurodegenerative disorders represent a significant source of mortality and disease in humans in the world today. Applicants believe the claimed HGRA4sv polynucleotide has a substantial utility and does not represent a throw-away utility.

In addition to a specific and substantial utility, as Applicants have asserted, the Revised Utility Examination Guidelines require that such utility be credible (a "credible utility"). That is, whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Such assertions are credible unless "(A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion." See, Revised Utility Guidelines Training Materials. Applicants believe that one skilled in the art of neurobiology, upon reviewing the totality of the evidence taught by Applicants specification, would logically arrive at the same conclusion as Applicants that HGRA4sv is a human glycine receptor family member and would have the utilities asserted by Applicants. Because Applicants have asserted specific and substantial utilities that are credible, Applicants have also complied with the credible utility requirement.

Further, PTO personnel are reminded that they must treat as true a statement of fact made by Applicants in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Significantly, no such countervailing evidence has been provided. If such evidence is available to the examiner, Applicants request that the Examiner provide an affidavit pursuant to 37 C.F.R. § 1.104(d)(2) containing evidence substantiating this position.

Applicants also wish to point out to the Examiner that the Utility requirement may be met by disclosure of a well-established utility for the claimed invention. A well-established utility is defined as a "specific utility" which is well-known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art (Revised Utility Examination Guidelines). Applicants have already asserted *supra* that HGRA4sv has a specific asserted utility. In addition, Applicants have also asserted *supra* that one skilled in the art would readily appreciate this utility based upon the teachings of Applicants specification. Furthermore, Applicants also assert that in consideration of

the teachings of Rappold-Hoerbrand in conjunction with Applicants specification, Applicants asserted utility for HGRA4sv is a well-established utility. Applicants assert that the utility requirement for the claimed invention has been met, and that Applicants invention is complete and that no additional research is required.

b. The Examiner also alleges that "the asserted utilities are not considered to be substantial because the specification fails to disclose any particular function, or biological significance *directly* associated with the instant HGRA4, nor any particular gene mutation, or any disease or condition associated with the HGRA4." (see page 3)

Applicants disagree and assert that the utilities asserted in Applicants specification are **directly** associated with the instant HGRA4 based upon the teachings of Rappold-Hoerbrand in conjunction with the evidence provided in Applicants specification as discussed *supra*. Since the HGRA4sv composition of the present invention represents a splice variant of HGRA4, Applicants assert that the asserted utilities are substantial, specific, and credible and that the utility requirement has been met.

c. The Examiner further alleges that "Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a known protein" (see page 3) and cites several publications to purportedly support the allegation.

Applicants do not refute the statements presented by the authors of the various cited publications. However, Applicants point out to the Examiner that not one of the authors state that predicting function based upon percent identity and/or similiarity is **never** accurate for every protein. Rather, the authors and even the Examiner acknowledge that such statements are generalities and do not hold true in every circumstance, but rather apply on a case-by-case basis. For example, Applicants point out to the Examiner the teachings of Attwood (Science., 290(5491):471-3 (2000)); submitted concurrently herewith) who acknowledges that function can be predicted based upon the presence of motifs that are essential for a particular function, stating "Gene family databases allow more specific functional diagnoses to be made than is possible by pairwise searching. They are based on the principle that related sequences can be aligned to find regions (motifs) that show little variation. These motifs usually reflect some vital structural or functional role...and they can be used

to derive diagnostic family signatures." (see page 472 under "Function prediction through pattern recognition" section). The latter is also supported by the teachings of Applicants specification based upon the presence of the conserved ligand binding sites, the conserved cysteines, the conserved transmembrane domains, the presence of the neurotransmitter gated ion channel domain, and the very high percent identity between HGRA4sv to known glycine receptors.

Re: Skolnick et al, Applicants do not refute that occasional assignment errors may occur when applying only homology comparisons to functional assignments. However, the lessons taught by Skolnick et al are not applicable to the instant case due to the convincing structural conservation of HGRA4sv with other glycine receptor proteins, and the conserved structure features discussed *supra*. As evidenced by the teachings of the instant specification, exceptions to Skolnick et al clearly exist. Applicants also assert that HGRA4sv does have a specific, substantial, credible, and well-established utility based upon the arguments presented *supra*.

The Examiner cites additional publications in support of the allegations discussed in the Action including Doerks et al., Smith et al., Brenner et al., Vukicevic et al., and Parnet et al. However, Applicants assert that these publications are not applicable to the claimed invention for the arguments presented *supra*. Applicants arguments are further enhanced by the fact that the claimed invention represents a splice variant of a well-characterized gene and is thus not subject to the Examiners arguments on homology and functional prediction, among others.

d. The Examiner also alleges that "In the instant case, applicants indicate that HGRA4 is structurally related to glycine receptor alpha subunits, which are known to form functional glycine receptor with other glycine receptor alpha subunits. However, an established utility for other glycine receptor alpha subunits cannot be automatically applied to HGRA4 without functional analysis."

Applicants disagree with the Examiners allegation and point out to the Examiner that in view of the teachings of Rappold-Hoerbrand and the undeniable association of HGRA4 to the incidence of ataxia, the Examiners argument is rendered moot since one skilled in the art would appreciate that when a gene is located at a chromsome locus, particularly a disease locus, that any splice variant of that gene would have the same utility since the splice variant is itself derived from the same gene.

e. The Examiner also alleges that "Even the instant specification indicates that the *exact* biological function should be tested, as stated on page 47, lines 10-13, that it is believed the encoded polypeptide may share at least some biological activities with glycine receptor alpha subunits, and a

number of methods of determining the *exact* biological function are known in the art or described elsewhere herein. While it is likely that the HGRA4 is a glycine receptor alpha subunit, that by itself does not suggest any substantial utility for the reasons above."

Applicants disagree with the Examiners allegations and point out to the Examiner that Applicants specification does, in fact, teach the exact physiological function of the HGRA4sv polynucleotide as discussed *supra*, in addition to teaching its intended utility as supported by the teachings of Rappold-Hoerbrand. Moreover, Applicants point out that the Examiner has taken Applicants statements out of context. Specifically, Applicants point out that one skilled in the art would appreciate that some genes and proteins have more than one biological function. As a result, Applicants should not be held to asserting only a single utility in the specification for any given polynucleotide. Rather, Applicants have contended that HGRA4sv likely has additional biological activity beyond the preferred activity that Applicants have asserted in the specification. Applicants intention was to encompass this possibility and to teach how one skilled in the art could determine such additional functions. Applicants assert that the claimed HGRA4sv does have a specific, substantial, credible, and well-established utility based upon the arguments presented *supra*.

f. The Examiner also alleges that "The disclosed uses in diagnosis and treatment are not substantial, in the absence of knowledge of any disease or condition associated with inappropriate HGRA4 activity or levels, which could be so treated. Therefore, there is no immediately evident patentable use for the HGRA4."

Applicants disagree and again point out the teachings of Applicants specification in view of the teachings of Rappold-Hoerbrand. Since HGRA4 has been positively associated with the incidence of ataxia, Applicants assert that the claimed HGRA4sv does have a specific, substantial, credible, and well-established utility based upon the arguments presented *supra*.

g. The Examiner also alleges that "The instant situation is analagous to that which was addressed in B*renner v. Manson*...in which a novel compound which was structurally analagous to other compounds which were known to possess anti-tumor activity was allegef to be potentially useful as an anti-tumor agent in the absence of evidence supportiung this utility...".

Applicants do not agree with the Examiners alleged application of Brenner v. Manson to the pending claims of the instant application. At issue in Brenner was whether a chemical process for synthesizing chemical compounds was patentable for an application that did not disclose any utility for the disclosed compounds. Specifically, only the chemical compound was disclosed and no statement on utility of this compound was made either explicitly or through reference to a publication, nor to the class of compounds that were orthologous to the claimed compounds at issue in the case. Applicants assert that the instant patent application explicitly discloses the utility of the HGRA4sv polynucleotide and polypeptides as originally filed. Thus, since the utility of HGRA4sv is already disclosed in the specification, Brenner v. Manson cannot apply.

h. The Examiner alleges "There is no evidence of record or any line of reasoning that would support a conclusion that said HGRA4sv [wsd]was, as of the filing date, useful for treatment of any disorders as stated at pages 44-47 of the specification. Until some actual functional property or specific relationship between gene mutations of HGRA4sv and diseases or conditions can be established, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility and the claimed invention is incomplete as of the filing date."

Applicants disagree and again point out the teachings of Applicants specification in view of the teachings of Rappold-Hoerbrand. Since HGRA4 has been positively associated with the incidence of ataxia, Applicants assert that the claimed HGRA4sv does have a specific, substantial, credible, and well-established utility based upon the arguments presented *supra.* Moreover, Applicants point out that there is no requirement that Applicants preferred or best utility be disclosed in a specific location or even exemplified as representing Applicants preferred or best utility. The Examiner suggests that Applicants be held to only those utilities stated on pages 44-47. According to the MPEP (608.01(h)), "There is no statutory requirement for the disclosure of a specific example. A patent specification is not intended nor required to be a production specification. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1536, 3 USPQ2d 1737, 1745 (Fed. Cir. 1987); *In re Gay*, 309 F.2d 768, 135 USPQ 311 (CCPA 1962). The absence of a specific working example is not necessarily evidence that the best mode has not been disclosed..." As evidenced above, Applicants have clearly disclosed Applicants utility in addition to the utility that was corroborated by the teachings of Rappold-Hoerbrand in Applicants specification as originally filed.

III. Rejections under 35 U.S.C. § 112, First Paragraph

a. The Examiner has rejected claims 20 to 40 under 35 U.S.C. § 112, first paragraph. More particularly, the Examiner alleges that "since the claimed invention is not supported by either a specific, substantial, or credible utility...one skilled in the art clearly would not know how to use the claimed invention."

Applicants disagree. Applicants believe the Examiners allegations have been overcome in light of the arguments presented *supra*, the teachings of Applicants specification as originally filed, in addition to the teachings of Rappold-Hoerbrand. Since HGRA4sv has a specific, substantial, and well established utility in the specification as originally filed, one skilled in the art clearly would know how to use the claimed invention. In addition, Applicants also assert that since the HGRA4sv function and its biological significance are disclosed in the specification as originally filed, Applicants specification provides the requisite teachings that a skilled artisan would require to use the claimed invention.

b. The Examiner has rejected Claims 20(e), 20(f), 28, 29, and 37 under 35 U.S.C. § 112, first paragraph, alleging that "enablement would not be commensurate in scope with the claims, which encompass nucleic acid encoding a polypeptide 97% identical to SEQ ID NO:3 or the sequence encoding SEQ ID NO:4 (claim 37, for example), or fragments of the nucleic acid sequences encoding fragments of SEQ ID NO:4 (claim 20, part (e), and claims 28 and 29, for example), and antisense polynucleotide (claim 20, part (f))...The specification does not teach how to use nucleic acid variants or fragments. Since no specific biological function of the HGRA4sv is disclosed in the specification, and since one skilled in the art could not determine with a reasonable expectation of scussess, and without undue experimentation what a specific biological function of HGRA4sv would be, the skilled artisan would not be able to make the % variants, fragments or antisense, and test them for a biological activity, or loss thereof (by antisense for example)".

Applicants disagree with the Examiners allegation and assert that the instant specification does provide an enabling description for how to make an isolated nucleic acid which comprises an isolated polynucleotide that represents the antisense polynucleotide claimed in Claim 20(f). As the Examiner will appreciate, the claimed polynucleotides are double stranded with the top strand, also referred to as the sense strand, serving as the coding strand for the HGRA4sv sequences. The

complementary sequence of a sequence is simply its antisense, or complementary strand, of the sense strand. Thus, a skilled artisan would only need to know the sense strand of a particular sequence to identify the complementary sequence. Once that complementary sequence is known, one skilled in the art would only need to synthesize the sequence using methods well known in the art. Methods for making complementary sequences for polynucleotide sequences are well-known in the art (see Stein et al., Nucl. Acids Res., 16:3209 (1988); and Okano, Neurochem., 56:560 (1991); submitted concurrently herewith). Moreover, Applicants specification provides detailed teachings on how one skilled in the art could make and use complementary sequences of the present invention (see pages 199 to 205, for example). Applicants attribute the Examiners rejection of Claim 20(f) primarily to the "or fragment thereof" limitation. In the interest of facilitating prosecution, Applicants have amended Claim 20(f) to delete the "or fragment thereof" limitation. Applicants believe the Examiner's rejection has been rendered moot in light of this amendment. Since Claim 30 depends from Claim 20(f), the Examiners rejection of Claim 30 has also been rendered moot. Moreover, since Claims 31, 32, 33, 34, 35, 36, 37, 38, 39, and 40 depend from Claim 20, the Examiners rejection of these claims as they relate to Claim 20(f) has also been rendered moot.

Applicants also disagree with the Examiners allegation relative to Claim 20(e) and its dependent Claims 28 and 29 and assert that the instant specification does provide an enabling description for how to make an isolated polynucleotide encoding at least 225 contiguous amino acids of SEQ ID NO:4. However, Applicants have amended Claim 20(e) to add the "wherein said encoded polypeptide has glycine receptor activity" limitation for the sole purpose of facilitating prosecution. Applicants believe the Examiner's rejection has been rendered moot in light of this amendment. Since Claims 28 and 29 depend from Claim 20(e), the Examiners rejection of Claims 28 and 29 have also been rendered moot. Applicants reserve the right to prosecute these claims in their original form in related applications.

Applicants also disagree with the Examiners allegation relative to Claim 37 and assert that the instant specification does provide an enabling description for how to make an isolated polynucleotide having a nucleotide sequence at least 97% identical to a sequence provided in Claim 20. Applicants assert that one skilled in the art could make and use the invention embraced by Claim 37 based upon the teachings of the Applicants specification. Applicants wish to point out to the Examiner that Claim 37 is limited to a polynucleotide that has at least "97% identity to a sequence provided in Claim 20" wherein percent identity is calculated using a CLUSTALW global sequence alignment". As discussed *infra*, the global sequence alignment limitation is significant since it

requires that the percent identity be based upon the **entire** length of each sequence in comparison to the **entire** length of a comparison sequence as determined using CLUSTALW. This type of alignment is referred to as a global sequence alignment and is distinguished from a local alignment, as would be produced using the BLAST alignment program. For example, the BLAST algorithm does not take into account the entire length of each sequence compared, but rather only the specific local regions that share identity. Applicants point out to the Examiner the teachings of the subject specification on pages 66-72 that define percent identity.

Briefly, for a sequence to be considered 97% identical to a sequence of Claim 37, a sequence would need to have as few as 3 nucleotides per 100 nucleotides or less that are different from the subject sequence. Alternatively, a sequence encompassed by Claim 37 could either be slightly shorter or longer than a sequence provided in Claim 20, or have a combination of nucleotide changes and terminal or internal deletions, additions, etc., that would equate to 97% identity or greater. Applicants point out to the Examiner that methods of introducing mutations in a particular nucleotide sequence are well known in the art and that the skilled artisan would be able to make and use the invention simply based upon the teachings of Applicants specification.

According to Cunningham and Wells (Science 244:1081-1085 (1989)); submitted concurrently herewith), proteins are surprisingly tolerant of amino acid substitutions (see page 74). Applicants assert one skilled in the art would acknowledge the minimal impact on a proteins function by introducing such low numbers of alterations in its sequence, particularly in view of Cunningham and Wells. Applicant's assertion is supported by the fact that a number of these nucleotide sequence substitutions would encode amino acids that are structurally and biochemically similar enough to the native amino acid residues at each position along the HGRA4sv polypeptide so as to enable the mutated protein to retain native function. Such amino acid substitutions are referred to as "conservative substitutions". Applicant's specification teaches the accepted conservative substitutions known in the art in Table III. According to Cunningham et al above, such conservative substitutions are likely to be phenotypically silent. Applicant's specification not only provides Table III that exemplifies accepted conservative substitutions, but also specifically teaches how one skilled in the art could create sequences that would fall within the scope of Claim 37 (see pages 72 to 78, and Example 22). Applicant's specification also explicitly discloses N- and C-terminal deletion mutants of the HGRA4sv polypeptide (see pages 48-53), in addition to teaching how one skilled in the art could create such mutants in Example 23. Some of these mutants are clearly encompassed by

the scope of Claim 37. Clearly one skilled in the art would know how to make and use the invention embraced by Claim 37 based upon the teachings of Applicant's specification.

However, Applicants have amended Claim 37 to append the "wherein said polynucleotide further encodes a polypeptide having glycine receptor activity" limitation for the sole purpose of facilitating prosecution. Applicants believe the Examiner's rejection has been rendered moot for Claim 37 in light of this amendment. Applicants expressly assert that Claim 37 was amended for the sole purpose of facilitating prosecution, and not in an effort to overcome any 35 U.S.C. §112, first paragraph rejections. Since Claims 38, 39, and 40 depend from Claim 37, the Examiners rejection of these claims as they relate to Claim 37 has also been rendered moot. Moreover, since Claim 37 depends from Claim 20, Applicants amendments to Claims 20(e) and 20(f) also render the Examiners rejection of Claim 37 moot, in part, as well. Applicants reserve the right to prosecute these claims in their original form in related applications.

c. The Examiner has further rejected Claim 37 under 35 U.S.C. § 112, first paragraph, alleging that it contains "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention...The claim does not require that the polypeptide possess any particular distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity."

Applicants expressly disagree with the Examiners allegation and point out that applicants have clearly disclosed explicit sequences that meet the 97% identity limitation of Claim 37 (N- and C-terminal deletion mutants provided on pages 48-53). Clearly Applicants were in possession of these sequences based upon the explicit disclosure of the same. Applicants also point out the amendments to Claim 37 *supra*. Applicants believe the Examiners rejection of Claim 37 has been overcome in light of these amendments, in addition to the express teaches of Applicants specification. Since Claims 38, 39, and 40 depend from Claim 37, the Examiners rejection of these claims as they relate to Claim 37 has also been rendered moot. Moreover, since Claim 37 depends from Claim 20, Applicants amendments to Claims 20(e) and 20(f) also render the Examiners rejection of Claim 37 moot, in part, as well.

Applicants also assert that the Examiners rejections specific to the application of *Vas-Cath Inc. v. Mahurkar* and *Fiddes v. Baird* have also been rendered moot in light of Applicants arguments described herein.

d. The Examiner has further rejected Claim 20 under 35 U.S.C. § 112, first paragraph, alleging that it contains "subject matter which was not described in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention...Claim 20 states a deposit of a cDNA clone encoding said protein contained in ATCC Deposit No. PTA-2966. However, the specification fails to provide the deposit statement indicating the desposit material will be readily available to the public without restriction upon issuance of the patent."

In response, Applicants point out the statement provided in section I(a) *supra*. Applicants believe the provided statement adequately overcomes the Examiners rejection of Claim 20.

IV. Rejections under 35 U.S.C. § 112, second paragraph

a. The Examiner has rejected Claims 20 to 40 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner has rejected Claim 20 as being "indefinite for the recitation of 'the complimentary sequence (antisense)'" stating specifically that is "unclear whether "antisense" in the parentheses is a part of the limitation of the claim, and if so, what limitation is imported by such. For example, does it eliminate other possible complimentary sequences such as complimentary DNA sequence (from the complimentary strand)? Therefore, the metes and bounds of the claim cannot be determined".

Applicants disagree and point out to the Examiner that the purpose of including the term 'antisense' in parentheses was only meant to emphasize Applicants intention to claim the complementary strand of the sequences embraced by Claims 20(a) to (e). The inclusion of the 'antisense' term was not intended to append an additional limitation over and beyond that provided by the 'complementary' term. Since the use of the 'antisense' term was not meant to be further limitating, but rather was only included to clarify the limitation imposed by the 'complementary' term, Applicants have deleted the "(antisense)" term from Claim 20(f). Since Claims 21 thru 40 depend from Claim 20, Applicants believe the Examiner's rejection has been rendered moot in light of this amendment as it relates to Claim 20(f).

b. The Examiner has rejected Claim 37 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More particularly, the Examiner has rejected Claim 37 as being

"indefinite for reciting a specific computer program 'CLUSTALW global sequence alignment' as the claim does not specify the version number, and what parameters are to be used. Deletion of such a limitation is suggested as it adds no patentable weight to the claimed nucleic acid".

Applicants disagree with the Examiners allegation that the 'CLUSTALW global sequence alignment' limitation does not import any patentable weight to the claimed nucleic acid. Specifically, Applicants point out to the Examiner that the inclusion of this limitation defines the metes and bounds of this claim and that deletion of this limitation would affect the scope of this claim. Applicants point out to the Examiner that CLUSTALW has a "fixed and definite meaning" in the art and that Applicants use of the CLUSTALW limitation was not arbitrary, since Applicants specification clearly, and unambiguously, provides the citation for this algorithm (see page 68, Thompson, J.D., et al., Nucleic Acids Research, 2(22):4673-4680, (1994)), in addition to defining the parameters to use when applying this algorithm (see "Preferred parameters used in a CLUSTALW alignment..." on page 68, line 12). It should be noted that various global sequence alignment algorithms are known in the art, and include, for example GAP, PRETTY, FASTA, Needleman-Wunsch, etc. Application of each of these algorithms to aligning two or more sequences would each result in different percent identity values, which may or may not be the same as the percent identity value provided by application of the CLUSTALW algorithm. Thus, Applicants further assert that the inclusion of the CLUSTALW limitation in Claim 37 is essential to defining Applicants invention since the public would not be able to assess the metes and bounds of this claim without knowing what global sequence alignment algorithm to apply.

The Examiners request that the version number and parameters used be added to Claim 37 is noted. In response, Applicants have appended the version number and parameters outlined in the specification to Claim 37. Applicants believe the Examiners rejection has been rendered moot in light of this amendment. Since Claims 37 thru 40 depend from Claim 37, Applicants believe the Examiner's rejection has also been rendered moot for Claims 37 thru 40 in light of this amendment.

V. Rejections under 35 U.S.C. § 102(b).

a. The Examiner has rejected Claims 20 and Claims 30 thru 32 under 35 U.S.C. § 102(b) as being anticipated by Grenningloh et al (EMBO J. 1990 Mar;9(3):771-6). Specifically, the Examiner alleges that "Grenningloh discloses a nucleic acid sequence (locus HSGLYRA1, Figure 1), which encodes a glycine receptor alpha subunit, and comprises nucleotide sequence encoding amino acid residues 247-302 of the instant SEQ ID NO:4 with 100% identity (see the computer

search result printout). Further, Grenningloh's nucleic acid is a cDNA clone (page 771, the right column), indicating the double strand of the molecule, and hence the complementary sequence thereof. Although Grenningloh's nucleic acid sequence does not encode the entire sequence of the present SEQ ID NO:4, the nucleotide *fragment* encoding the cited amino acid fragment meets the limitation of "fragment thereof" in part (f) of claim 20, and claim 30, and is a "fragment thereof". As such, the reference anticipates claims 20 and 30. Additionally, the reference teaches an expression vector containing the nucleic acid, a1-pCIS2 or pSPT19, and a host cell comprising the vector, HEK-293 (page 773). The reference, therefore, also anticipates claims 31 and 32."

Applicants disagree. However, Applicants have deleted the "or fragment thereof" limitation of Claim 20(f) in the sole interest of facilitating prosecution. Since Claim 30 depends from Claim 20(f) specifically, and since Claims 31 and 32 depend from Claim 20, generally, Applicants believe the Examiners rejection has been rendered moot in light of this amendment. Applicants reserve the right to prosecute this claim in its original form in related applications.

VI. Rejections under 35 U.S.C. § 102(a).

a. The Examiner has rejected Claims 20 and Claims 30 thru 32 under 35 U.S.C. § 102(a) as being anticipated by Rappold-Hoerbrand, WO 00/58461. Specifically, the Examiner alleges that Rappold-Hoerbrand discloses a nucleic acid sequence, SEQ ID NO:1, which encodes a human ataxia protein having SEQ ID NO:3 with 100% sequence identity (see the computer sequence search result printout). Further, the reference teaches that said nucleic acid sequence is a cDNA sequence indicating the double strand of the molecule, and hence the complimentary sequence thereof. Although Grenningloh's nucleic acid sequence does not encode the entire sequence of the present SEQ ID NO:4, the nucleotide *fragment* encoding the cited amino acid fragment meets the limitation of "fragment thereof" in part (f) of claim 20, and claim 30, and is a "fragment thereof". As such, the reference anticipates claims 20 and 30. Additionally, the reference teaches a recombinant vector and host cell containing the isolated nucleic acid (the paragraph bridging pages 9 and 10, and claims 7 and 8), and the reference, therefore, also anticipates claims 31 and 32."

Applicants disagree. However, Applicants have deleted the "or fragment thereof" limitation of Claim 20(f) in the sole interest of facilitating prosecution. Since Claim 30 depends from Claim 20(f) specifically, and since Claims 31 and 32 depend from Claim 20, generally, Applicants believe the Examiners rejection has been rendered moot in light of this amendment. Applicants reserve the right to prosecute this claim in its original form in related applications.

VII. Rejections under 35 U.S.C. § 103(a).

a. The Examiner has rejected Claims 34 thru 36 under 35 U.S.C. § 103(a) as being "unpatentable over Grenningloh et al. (EMBO J. 1990 Mar; 9(3):771-6), or Rappold-Hoerbrand, WO 00/58461, as applied to claims 20 and 30-32 above, and further in view of Capon et al., US5,116,964."

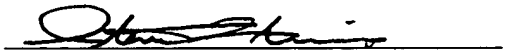
Applicants disagree. However, Applicants have deleted the "or fragment thereof" limitation of Claim 20(f) in the sole interest of facilitating prosecution. Since the Examiners rejection hinges upon the combination of the limitations taught in Grenningloh et al. and/or Rappold-Hoerbrand with those of Capon et al., Applicants believe the Examiners rejection of Claim 20(f) has been rendered moot in consideration of this amendment since not all of the limitations of Claims 34 thru 36 are taught by any of the references alone. Applicants reserve the right to prosecute this claim in its original form in related applications.

Applicants believe that all of the Examiners rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

A three-month extension is hereby requested pursuant to 37 CFR §1.136(a). Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $950 for payment of the extension fee.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,



Stephen C. D'Amico
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Reg. No. 46,652

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Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
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Date: February 19, 2004

D0079

ATCC

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Bristol-Myers Squibb Company
Attn: John Feder
P.O. Box 5400
Princeton, NJ 08543

MAR 01 2004

Deposited on Behalf of: Bristol-Myers Squibb Company

Identification Reference by Depositor:
Human cDNA inserts cloned into vector pSPORT; gene names are-HGPRBMY8, HGPRBMY23, BMY-HPP5, HGPRBMY7, CGR1, K+betaM2, K+alphaM1 (FL): BMS Group B

Patent Deposit Designation
PTA-2966

The deposit was accompanied by: __ a scientific description _ a proposed taxonomic description indicated above.

The deposit was received January 24, 2001 by this International Depository Authority and has been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested January 31, 2001. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Tanya Nunnally, Patent Specialist, Patent Depository

Date: February 5, 2001

cc: Stephen Damico
(Ref: Docket or Case No.: D0044, D0047, D0077, D0072, D0079, D0076, D0050)

Exhibit A

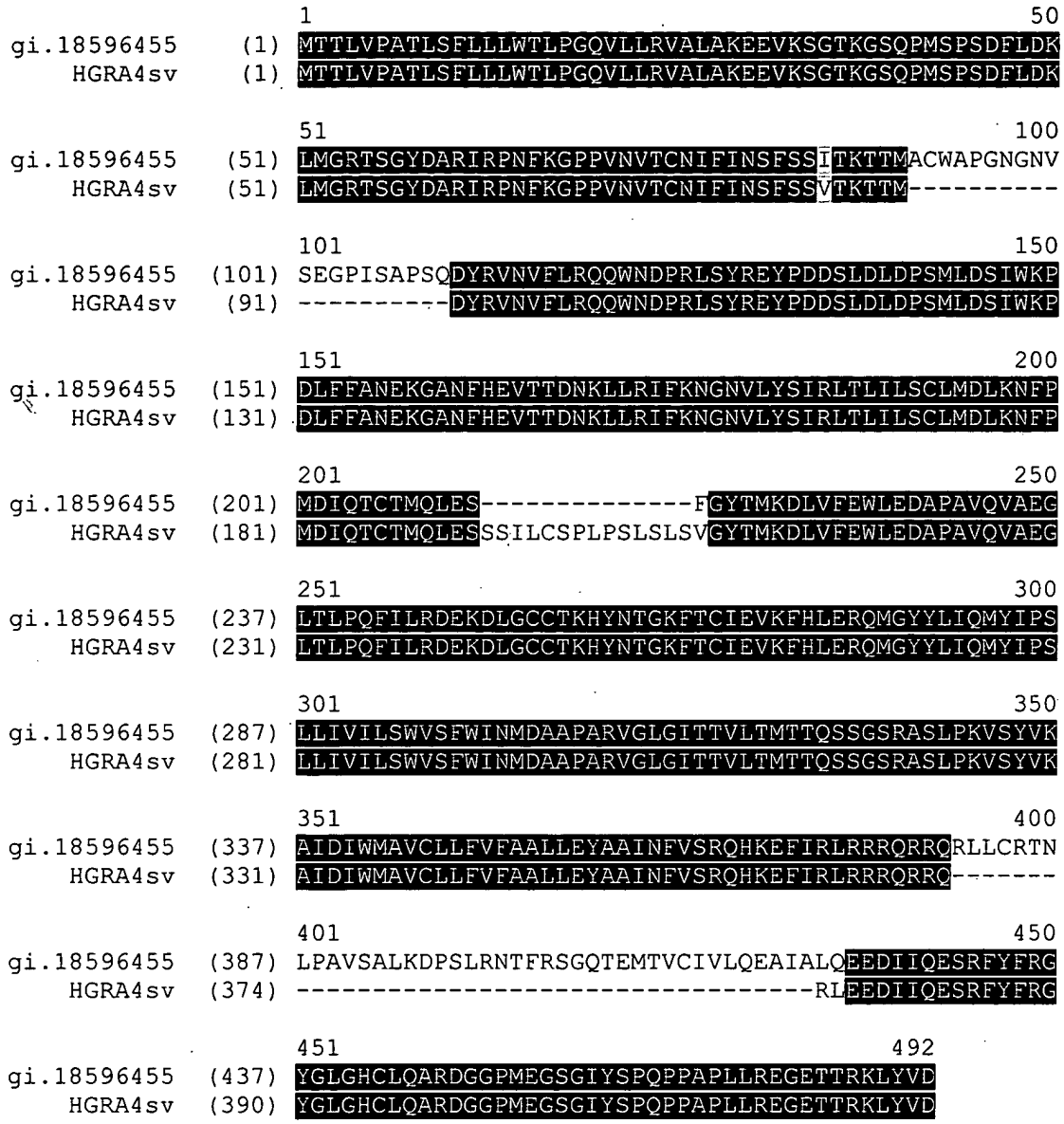
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Exhibit B

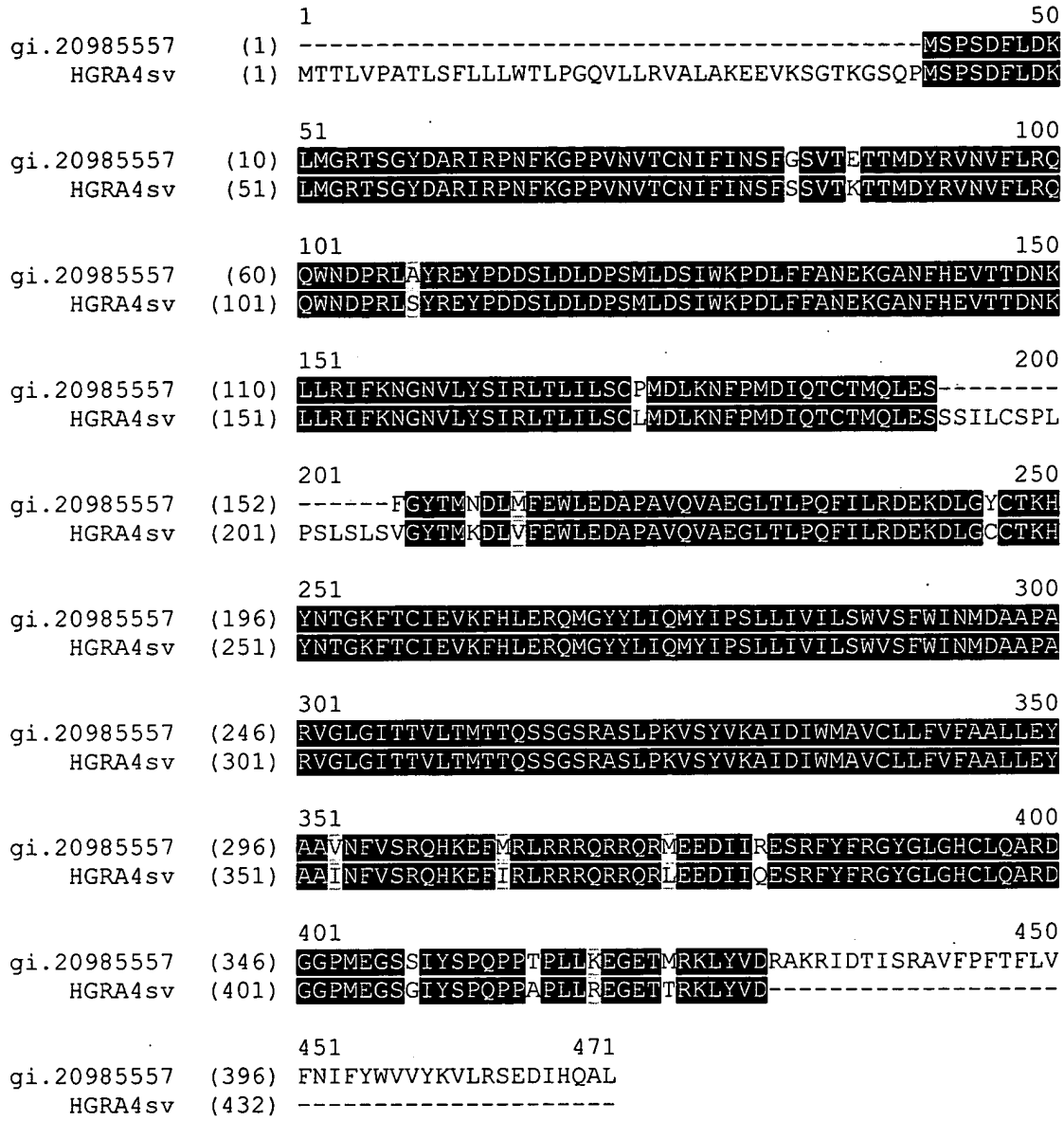
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Exhibit C

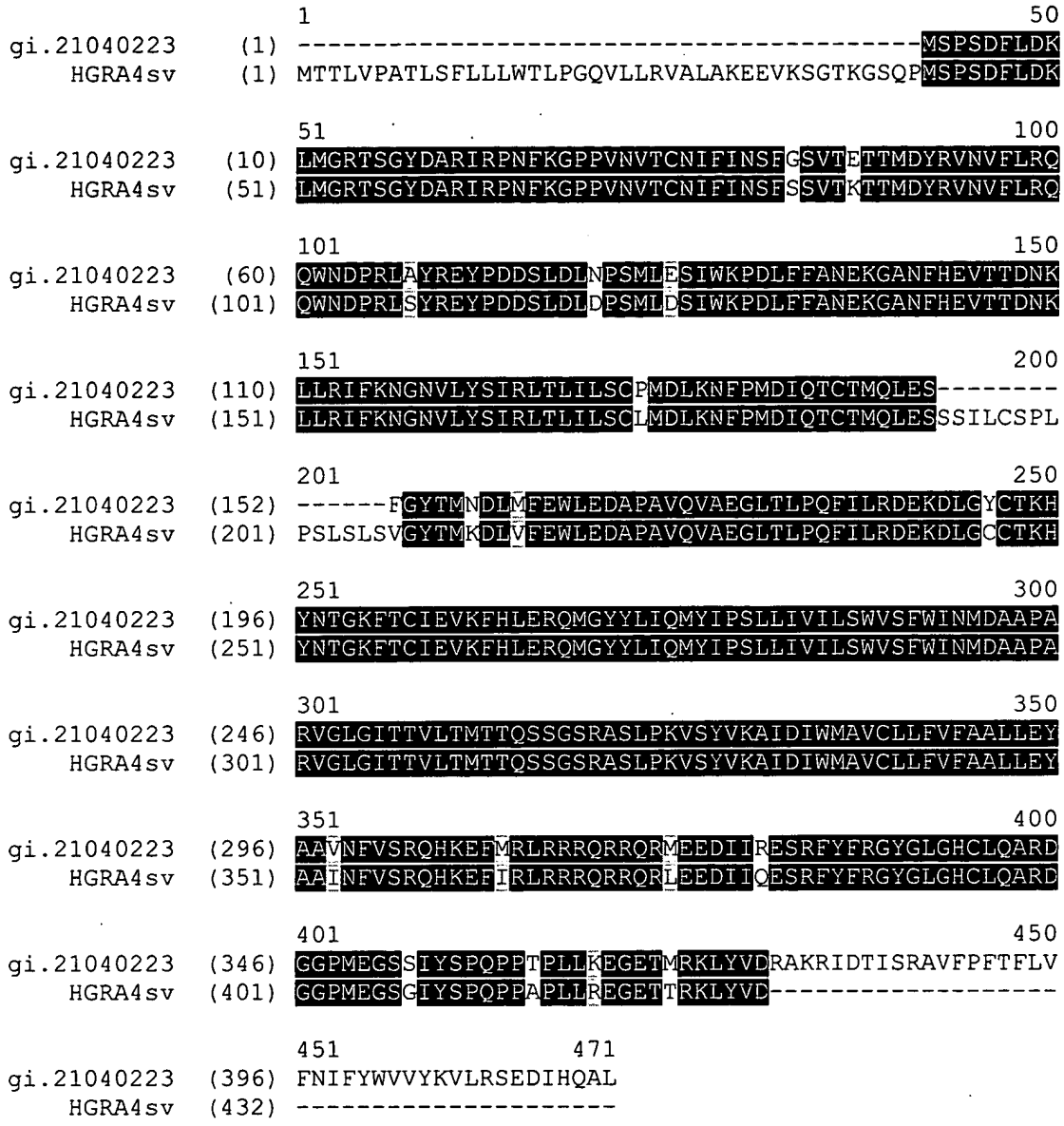
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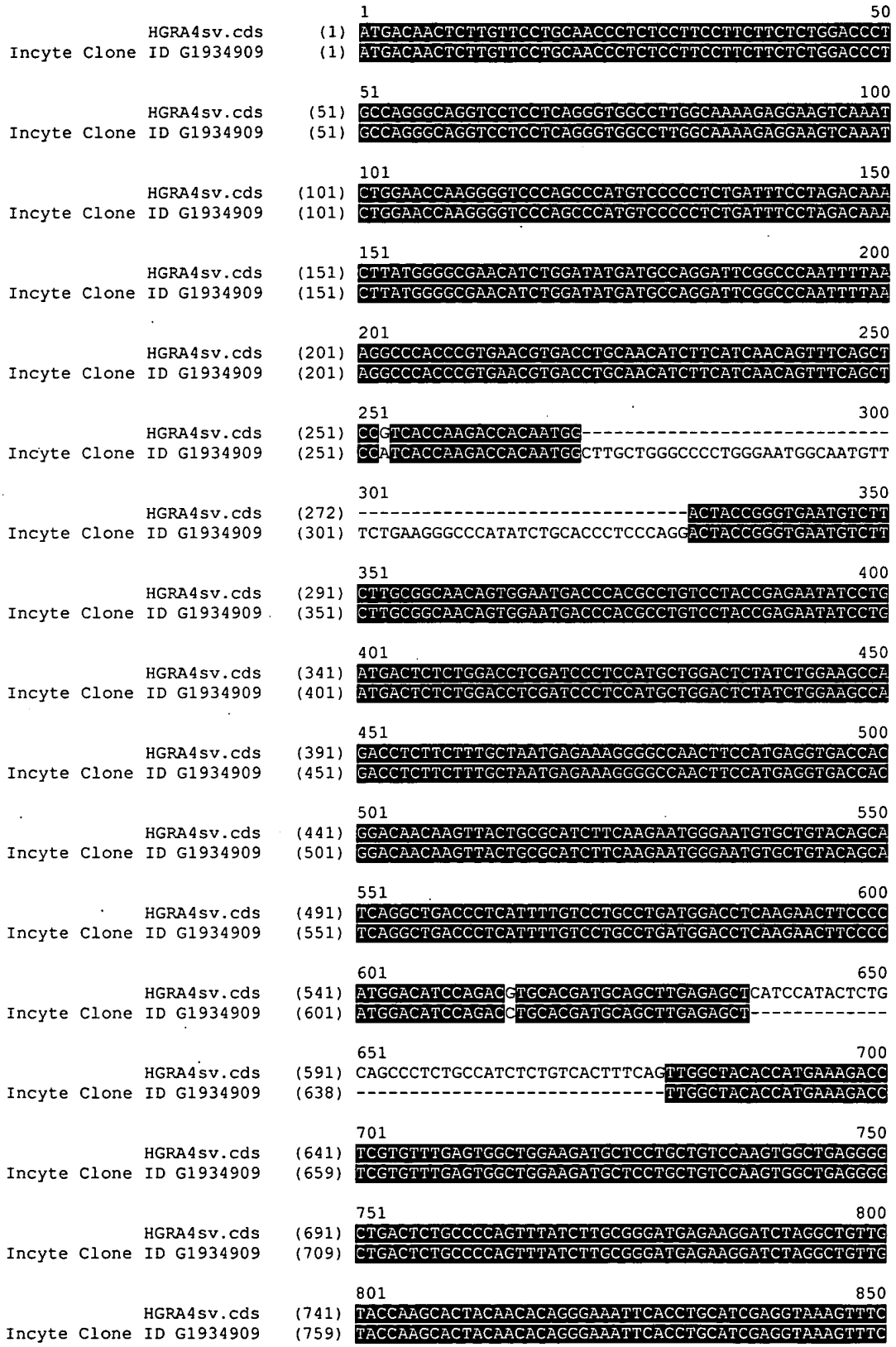
Exhibit D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Incyte Clone ID G1934909 (251) CCATCACCAAGACCACAATGGCTTGCTGGGCCCCTGGGAATGGCAATGTT
301 350
HGRA4sv.cds (272) ----------ACTACCGGGTGAATGTCTT
Incyte Clone ID G1934909 (301) TCTGAAGGGCCCATATCTGCACCCTCCCAGGACTACCGGGTGAATGTCTT
351 400
HGRA4sv.cds (291) CTTGCGGCAACAGTGGAATGACCCACGCCTGTCCTACCGAGAATATCCTG
Incyte Clone ID G1934909 (351) CTTGCGGCAACAGTGGAATGACCCACGCCTGTCCTACCGAGAATATCCTG
401 450
HGRA4sv.cds (341) ATGACTCTCTGGACCTCGATCCCTCCATGCTGGACTCTATCTGGAAGCCA
Incyte Clone ID G1934909 (401) ATGACTCTCTGGACCTCGATCCCTCCATGCTGGACTCTATCTGGAAGCCA
451 500
HGRA4sv.cds (391) GACCTCTTCTTTGCTAATGAGAAAGGGGCCAACTTCCATGAGGTGACCAC
Incyte Clone ID G1934909 (451) GACCTCTTCTTTGCTAATGAGAAAGGGGCCAACTTCCATGAGGTGACCAC
501 550
HGRA4sv.cds (441) GGACAACAAGTTACTGCGCATCTTCAAGAATGGGAATGTGCTGTACAGCA
Incyte Clone ID G1934909 (501) GGACAACAAGTTACTGCGCATCTTCAAGAATGGGAATGTGCTGTACAGCA
551 600
HGRA4sv.cds (491) TCAGGCTGACCCTCATTTTGTCCTGCCTGATGGACCTCAAGAACTTCCCC
Incyte Clone ID G1934909 (551) TCAGGCTGACCCTCATTTTGTCCTGCCTGATGGACCTCAAGAACTTCCCC
601 650
HGRA4sv.cds (541) ATGGACATCCAGACGTGCACGATGCAGCTTGAGAGCTCATCCATACTCTG
Incyte Clone ID G1934909 (601) ATGGACATCCAGACCTGCACGATGCAGCTTGAGAGCT----------
651 700
HGRA4sv.cds (591) CAGCCCTCTGCCATCTCTGTCACTTTCAGTTGGCTACACCATGAAAGACC
Incyte Clone ID G1934909 (638) ----------TTGGCTACACCATGAAAGACC
701 750
HGRA4sv.cds (641) TCGTGTTTGAGTGGCTGGAAGATGCTCCTGCTGTCCAAGTGGCTGAGGGG
Incyte Clone ID G1934909 (659) TCGTGTTTGAGTGGCTGGAAGATGCTCCTGCTGTCCAAGTGGCTGAGGGG
751 800
HGRA4sv.cds (691) CTGACTCTGCCCCAGTTTATCTTGCGGGATGAGAAGGATCTAGGCTGTTG
Incyte Clone ID G1934909 (709) CTGACTCTGCCCCAGTTTATCTTGCGGGATGAGAAGGATCTAGGCTGTTG
801 850
HGRA4sv.cds (741) TACCAAGCACTACAACACAGGGAAATTCACCTGCATCGAGGTAAAGTTTC
Incyte Clone ID G1934909 (759) TACCAAGCACTACAACACAGGGAAATTCACCTGCATCGAGGTAAAGTTTC

Exhibit D (Cont'd)

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                                    851                                                 900
                HGRA4sv.cds   (791) ACCTGGAACGGCAGATGGGCTACTATCTGATTCAGATGTACATCCCCAGC
Incyte Clone ID G1934909      (809) ACCTGGAACGGCAGATGGGCTACTATCTGATTCAGATGTACATCCCCAGC

                                    901                                                 950
                HGRA4sv.cds   (841) CTACTCATCGTCATCCTGTCCTGGGTCTCCTTCTGGATCAACATGGATGC
Incyte Clone ID G1934909      (859) CTACTCATCGTCATCCTGTCCTGGGTCTCCTTCTGGATCAACATGGATGC

                                    951                                                1000
                HGRA4sv.cds   (891) TGCCCCTGCCCGTGTGGGCCTGGGCATCACCACCGTGCTCACCATGACCA
Incyte Clone ID G1934909      (909) TGCCCCTGCCCGTGTGGGCCTGGGCATCACCACCGTGCTCACCATGACCA

                                   1001                                                1050
                HGRA4sv.cds   (941) CCCAGAGCTCTGGCTCCCGGGCCTCTTTGCCTAAGGTGTCCTACGTGAAG
Incyte Clone ID G1934909      (959) CCCAGAGCTCTGGCTCCCGGGCCTCTTTGCCTAAG----------------

                                   1051                                                1100
                HGRA4sv.cds   (991) GCAATCGACATCTGGATGGCTGTGTGTCTGCTCTTTGTGTTCGCTGCCTT
Incyte Clone ID G1934909      (994) --------------------------------------------------

                                   1101                                                1150
                HGRA4sv.cds  (1041) GCTGGAGTATGCTGCCATAAATTTTGTTTCTCGTCAGCATAAAGAATTCA
Incyte Clone ID G1934909      (994) --------------------------------------------------

                                   1151                                                1200
                HGRA4sv.cds  (1091) TACGACTTCGAAGAAGGCAGAGGCGCCAACGCTTGGAGGAAGATATCATC
Incyte Clone ID G1934909      (994) --------------------------------------------------

                                   1201                                                1250
                HGRA4sv.cds  (1141) CAAGAAAGTCGTTTCTATTTCCGTGGCTATGGCTTGGGCCACTGCCTGCA
Incyte Clone ID G1934909      (994) --------------------------------------------------

                                   1251                                                1300
                HGRA4sv.cds  (1191) GGCAAGAGATGGAGGTCCAATGGAAGGTTCTGGCATTTATAGTCCCCAAC
Incyte Clone ID G1934909      (994) --------------------------------------------------

                                   1301                                                1350
                HGRA4sv.cds  (1241) CTCCAGCCCCTCTTCTAAGGGAAGGAGAAACCACGCGGAAACTCTACGTG
Incyte Clone ID G1934909      (994) --------------------------------------------------

                                   1351
                HGRA4sv.cds  (1291) GAC
Incyte Clone ID G1934909      (994) ---
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